MPEP Section 2163 provides that the analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed (*see*, e.g., *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art. The guidelines in Section 2163 themselves provide that "***[g]enerally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement.***" Information which is well known in the art need not be described in detail in the specification. *See*, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

Applicants submit herewith journal articles, in addition to those submitted with the last response, that show that, at the time the application was filed, the level of skill in the art to which the invention pertains was such that it is not necessary for Applicants to include a great deal of detail in the specification to demonstrate that they were in possession of the invention. At the time the application was filed, it was known by the skilled artisan that peptides related to those claimed can and have been used in radionuclide therapy to treat tumors in rat animal models and in human patients.

Rat Animal Model

Bugaj *et al. Nucl. Med. Biol. 28*: 327-334 (2001)

Using animal tumor models, Bugaj *et al.* evaluated the radiotherapeutic efficacy of the radiolabeled somatostatin analog CMDTPA-Tyr^3-octreotate: a compound related to the radiolabeled peptides claimed in the present invention. Bugaj *et al.* focused on the beta-emitting nuclide, ^{153}Sm, chelated to the somatostatin analog, CMDTPA-Tyr^3-octreotate. Bugaj *et al.* found that suppression of tumor growth rate was observed in all animals treated with ^{153}Sm-CMDTPA-Tyr^3-octreotate compared to

untreated controls. Greater inhibition of tumor growth was observed in animals that received multiple doses.

On page 332, column 2, of the Bugaj *et al.* article, it is mentioned that "[a]dditional studies are necessary to determine whether the high pancreatic uptake observed in rats will also be found in humans." Bugaj goes on to say that "[r]esults with other octreotate derivatives in primates, where no apparent pancreas uptake is observed in scintigraphs, suggest that this will not be the case." Applicants note, and the skilled artisan will recognize, that tumors in locations other than the pancreas may be treated using the compound reported by Bugaj *et al.* Moreover, studies have been indeed performed that show that compounds related to those disclosed by Bugaj *et al.*, and also related to those claimed in the instant invention, can be used to treat tumors in humans.

Human Studies: Beyond the Rat Animal Model

Paganelli *et al.*, *Cancer Biother. Radiopharm. 14*: 477 – 483 (1999)

When the instant application was filed, Paganelli *et al.* had already demonstrated that a compound related to the radiolabeled peptides claimed in the present invention, can be used to treat tumors in humans. Paganelli *et al.* reports the dosage, safety profile and therapeutic efficacy of ^{90}Y-labeled DOTA-[D-Phe^{1}-Tyr^{3}]-octreotide (DOTATOC) when patients with cancers expressing somatostatin receptors are treated with this compound. Paganelli *et al.* also showed that out of 5 patients that were treated, complete and partial tumor mass reduction was measured in 25% of patients, along with 55% showing stable disease and 20% showing progressive disease.

In a 2001 journal article, Paganelli *et al.* reported the results from treatment of 30 patients with DOTATOC. Paganelli *et al.*, *Eur. J. Nucl. Med. 28*: 426 – 434 (2001). Paganelli *et al.* demonstrated that complete or partial tumor mass reduction occurred in 23% of patients; 64% had stable and 13% progressive disease. Both of the reports by Paganelli *et al.* are congruent with the notion that compounds such as those claimed in the present invention can be used to treat tumors in humans.

Kwekkeboom *et al., Eur. J. Nucl. Med. 28*: 1319-1325 (2001)

Kwekkeboom *et al.* recognized and demonstrated that ^{177}Lu- and ^{111}In-labeled somatostatin analogs were effective in treating tumors in animal models. For example, when the somatostatin analog [DOTA^0,Tyr^3]octreotate, a compound related to the compound used by Paganelli *et al.*(*supra*) and to the compounds claimed in the present invention, was labeled with the beta- and gamma-emitting radionuclide ^{177}Lu, it had a favorable impact on tumor regression and animal survival in a rat model. Because of these advantages Kwekkeboom decided to compare [^{177}Lu-DOTA^0,Tyr^3]octreotate with [^{111}In-DTPA^0]octreotide in six *human* patients with somatostatin receptor-positive tumors. From their comparative experiments, Kwekkeboom *et al.* concluded that [^{177}Lu-DOTA^0,Tyr^3]octreotate demonstrated higher absorbed doses in most tumors, with about equal doses to potentially dose-limiting organs.

In addition to their own findings, Kwekkeboom *et al.* report a study by Otte *et al.* that showed that five human patients suffering from neuroendocrine tumors were treated successfully with [^{90}Y-DOTA^0-Tyr^3]octreotide. The Kwekkeboom *et al.* article also cites results of a study by Valkema *et al.* using [^{90}Y-DOTA^0-Tyr^3]octreotide treatment in a multicenter trial in 22 end-stage patients with progressive disease. Valkema *et al.*, *J. Nucl. Med. 41*: 111P (2000). Valkema *et al.* demonstrated that when these patients were treated with [^{90}Y-DOTA^0-Tyr^3]octreotide, a partial tumor response was observed in two patients, a minor response was observed in three patients and a stable disease was observed in ten patients.

The results from the journal articles described above show the level of skill in the art at the time the application was filed. The ordinary skilled artisan would therefore know how to use radiolabeled peptides, such as those disclosed and claimed in the present application, to treat tumors. Applicants assert, therefore, that it is not necessary to describe in the specification information which is well known in the art such as how the claimed peptides would be used to treat tumors. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). Accordingly, the instant specification not only complies with the written description requirement, but it also demonstrates that Applicants had possession of the

claimed invention.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

B. Rejections Based on 35 U.S.C. § 112, Second Paragraph

Claims 24 - 43 stand rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite.

1. Rejection based on the recitation of two statutory subject matters

The Examiner stated that claim 24 is confusing in that it covers two statutory subject matters: method of using and method of making.

Applicants respectfully note that they are not aware of any provision in the MPEP or U.S. Code that would preclude Applicants from claiming a method of using the claimed radiolabeled peptides to treat tumors, where the radiolabeled peptides are characterized by the way they are made. Further, Applicants are not aware of any provision in the MPEP or U.S. Code that would render such a claim indefinite. In the instant Office Action, the Examiner asserts that the general rule is found in the case law. *In re Johnson*, 157 USPQ 620, 623 (CCPA 1968).

Applicants respectfully offer that *In re Johnson* does not support the Examiner's contention that a claim directed to a method of using a compound is indefinite if it also contains language that corresponds to the method of making the compound. In *In re Johnson*, the Court of Customs and Patent Appeals held that claim 1, in the Application of Johnson, was definite under 35 U.S.C. § 112, second paragraph, notwithstanding the fact that claim 1 recited "[a] relatively detailed description of the physical structure of the article . . . followed by a description of the process steps which were carried out in order to create the article." *Id.* at 622. The Court did not see why "further limitations defining the process of producing the article should be automatically fatal to the claims any more than the addition of further structural limitations would be." *Id.* at 622.

While not acquiescing to the Examiner's position on the alleged indefiniteness of claims 24 – 43, and simply in an effort to expedite the prosecution of the instant Application, Applicants have amended claim 24 such it does not recite alleged process steps that describe how the compound of claim 24 is made.

Reconsideration and withdrawal of the rejection of claim 24 under 35 U.S.C. § 112, second paragraph is respectfully requested.

2. Rejection Based on lack of clarity with respect to the term "together" in claim 24

The Examiner has withdrawn this rejection.

3. Rejection based on the term "lower" in claim 24

The Examiner alleges that the term "lower" in "lower alkyl" is a relative term. The Examiner has suggested that Applicants recite the number of carbon atoms contained therein. The Examiner has also suggested that Applicants recite the number of carbon atoms contained in the aryl and cycloalkyl groups.

Applicants are still of the opinion that it is not necessary to amend claim 24 to recite the number of carbon atoms in the lower alkyl, aryl and cycloalkyl groups, as the specification clearly describes the number of carbon atoms in each of the aforementioned groups at page 11, lines 7 - 23. Thus, the terms lower alkyl, aryl and cycloalkyl are indeed definite, as they are clearly described in the specification at the aforementioned page and line numbers.

Never the less, while not acquiescing to the Examiner's position on the alleged indefiniteness of claims 24 – 43, and simply in an effort to expedite the prosecution of the instant Application, Applicants have amended claim 24 in a manner that in no way limits the scope of claims 24 – 43. In particular, Applicants have amended claim 24 to recite the carbon ranges in the recitations of the terms lower alkyl, aryl and cycloalkyl. Applicants assert that this amendment in no way limits the scope of claims 24 – 43 since the carbon ranges were found in the Specification to begin with (*supra*).

Reconsideration and withdrawal of the rejection of claim 24 under 35 U.S.C. §

112, second paragraph is respectfully requested.

4. Rejection based on the phrases "a protecting group that can be removed under the conditions of peptide synthesis" and "then contacting said solution with a radionuclide and recovering the radiolabeled peptide" in claim 24

In the previous Office Action, the Examiner asserted that in claim 24, it is not clear whether the compound administered is in protected or non-protected form. In the instant Office Action, the Examiner explains that the issue at hand is, once again, that a claim may not contain a physical structure of a compound and process steps which were carried out in order to make the compound. In support of this rejection, the Examiner once again cites the holding in *In re Johnson*.

As noted above in Section 1 of this Response, *In re Johnson* holds that there is no reason why "the addition of further limitations defining the process of producing the article should be automatically fatal to the claims any more than the addition of further structural limitations would be," vis-à-vis the definiteness of the claim. *In re Johnson* 157 USPQ at 622. Thus, Applicants should be able to claim compounds by the way they are made, so long as the limitations do not in any way "obscure or confuse the structure of the article," or compound, as the case may be. *In re Johnson*, 157 USPQ 620, 622 (CCPA 1968).

While not acquiescing to the Examiner's position on the alleged indefiniteness of the phrases "a protecting group that can be removed under the conditions of peptide synthesis" and "then contacting said solution with a radionuclide and recovering the radiolabeled peptide" in claim 24, and simply in an effort to expedite the prosecution of the instant Application, Applicants have amended claim 24 such it no longer recites an alleged process step that describes how the compound is made, namely, "then contacting said solution with a radionuclide and recovering the radiolabeled peptide." Further, Applicants have amended claim 24 to simply recite "a protecting group," as opposed to "a protecting group that can be removed under the conditions of peptide synthesis."[♣]

[♣] The Specification, at page 18, lines 17 – 25 describes a number of protecting groups "that can be removed under the conditions of peptide synthesis," namely, Fmoc, Cbz, Boc and Aloc.

Reconsideration and withdrawal of the rejection of claim 24 under 35 U.S.C. § 112, second paragraph is respectfully requested.

5. Rejection of claim 44

The Examiner has withdrawn this rejection.

6. Rejection of claim 41

The Examiner has withdrawn this rejection.

III. CONCLUSION

Applicants acknowledge the Examiner's statement on page 6 of the Office Action dated July 31, 2002, that claims 24 – 44 (sic: 43) are free of the prior art. Thus, the claim amendments place the claimed invention in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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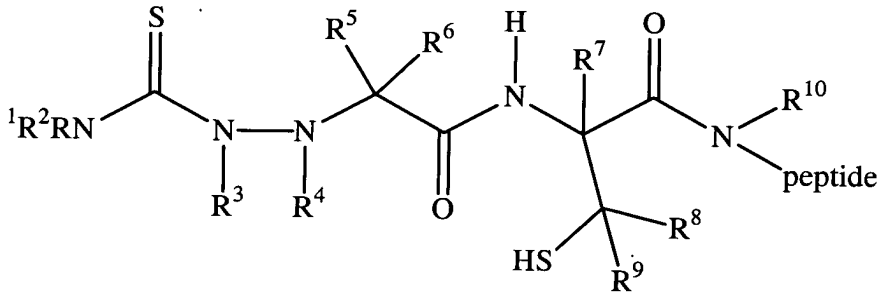
Version with Markings to Show Changes Made

IN THE CLAIMS:

24. (Amended) A method of treating a tumor, comprising administering to a human patient a radiolabeled peptide and a pharmaceutically acceptable carrier,

~~wherein said radiolabeled peptide is prepared by contacting a solution of a peptide with stannous ions,~~ wherein said peptide comprises a radiometal-binding moiety comprising the structure:



wherein R^1, R^2, and R^3 independently are selected from the group consisting of H, C_1-C_6 ~~lower~~ alkyl, substituted C_1-C_6 ~~lower~~ alkyl, C_3-C_6 cycloalkyl, substituted C_3-C_6 cycloalkyl, heterocycloalkyl, C_6-C_{12} aryl, C_6-C_{12} substituted aryl, heteroaryl, substituted heteroaryl, alkaryl, and a protecting group ~~that can be removed under the conditions of peptide synthesis~~, provided that at least one of R^1, R^2, or R^3 is H,

R^5, R^7, R^8, R^9 and R^{10} independently are selected from the group consisting of H, C_1-C_6 ~~lower~~ alkyl, substituted C_1-C_6 ~~lower~~ alkyl, C_6-C_{12} aryl, and substituted C_6-C_{12} aryl, and R^8 and R^9 together or R^7 and R^9 together may form a cycloalkyl or substituted cycloalkyl ring,

R^4 and R^6 together form a direct bond or are independently selected from the group consisting of C_1-C_6 ~~lower~~ alkyl, substituted C_1-C_6 ~~lower~~ alkyl, C_6-C_{12} aryl, and substituted C_6-C_{12} aryl, and wherein NR^{10} is located at the N-terminus of said peptide, or is located on an amino acid side chain of said peptide~~,~~

~~and then contacting said solution with a radionuclide and recovering the radiolabeled peptide~~.